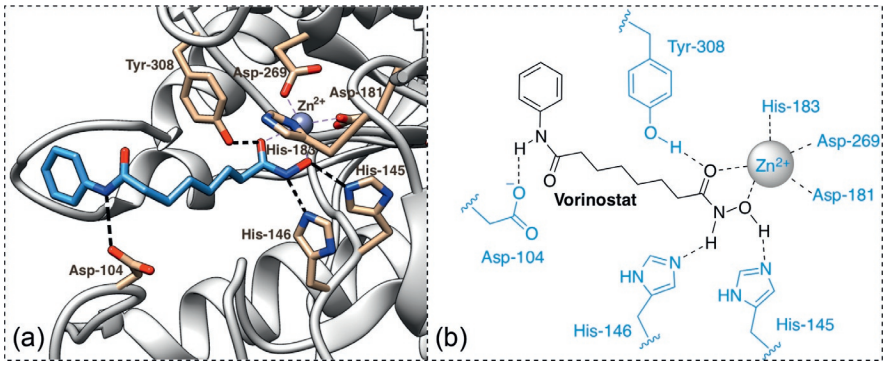

FIGURE 8.15

Interaction of vorinostat with the human HDAC2 active site. The three-dimensional structure was generated from Protein Data Bank reference 4LXZ, and displayed with Chimera 1.8.1.

An additional hydrogen bond is formed between an Asp residue and the vorinostat amide NH group. The hydroxamic acid hydroxyl group replaces a Zn^{2+}-bound water molecule of the active structure, and additional Van der Waals contacts (not shown) are established between hydrophobic enzyme amino acid residues and the inhibitor lipophilic chain. A similar mode of interaction has been described for trichostatin A.[56]

3.3 CYCLIC TETRAPEPTIDES

Some cyclic tetrapeptides are potent inhibitors of HDACs. The best-known compound of this group is romidepsin (FK-228, FR-901228, Istodax®), a depsipeptide isolated from a *Chromobacterium* that was approved by the FDA in 2009 for cutaneous T-cell lymphoma,[57] although it was rejected in 2012 by the EMA. It also entered clinical studies for the treatment of chronic lymphocytic leukemia and AML.[58] Romidepsin is a prodrug that is activated inside the cells by glutathione. The four-carbon chain between the free sulfhydryl and the cyclic depsipeptide core of this reduced active drug (RedFK) forms a covalent disulfide bond with the only cysteine residue present in the HDAC pocket[59] (Figure 8.16).

Trapoxins A and B are hydrophobic cyclotetrapeptides isolated from the fungus *Helicoma ambiens* that contain pipecolinic acid and proline residues, respectively. They also have two phenylalanines and an unusual amino acid bearing a side chain that contains an epoxide group. These compounds are potent enzyme inactivators, but they are too toxic for clinical use. In view of their structures, it would be reasonable to think that they irreversibly inhibit HDACs through a covalent bond that involves its epoxy group.[60] However, the α-epoxyketone moiety is not essential for activity, as can be deduced from the structure of apicidin, a fungal metabolite with antiprotozoal activity that also inhibits HDACs through induction of the *p21WAF1/Cip1* gene.[61] Apicidin is under preclinical assays as an anticancer agent.[62] CHAP-31, a trapoxin B analog in which the epoxy group has been replaced with a hydroxamate function,[63] is also under preclinical assays.[64]